UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/569,873	09/04/2007	**Wei Cheng**	05-953-A5	9736

63572 7590 04/30/2009

MCDONNELL BOEHNEN HULBERT @ BERGHOFF LLP
300 SOUTH WACKER DRIVE
SUITE 3100
CHICAGO, IL 60606

EXAMINER	
BIANCHI, KRISTIN A	

ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
04/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,873	CHENG ET AL.	
	Examiner	Art Unit	
	KRISTIN BIANCHI	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *30-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☒ Claim(s) *1-29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/24/2006,08/25/2006 and 08/08/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-35 are pending in the instant application. Claims 30-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected subject matter. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference which anticipates one group would not render obvious the other. Claims 1-29 are rejected. Claims 1-29 are objected.

Information Disclosure Statements

The information disclosure statements filed on February 24, 2006, August 25, 2006 and August 8, 2008 were considered and signed copies of 1449 are enclosed herewith.

Election/Restrictions

Applicants' election with traverse of Group I, claims 1-29, and the species N-[4-chloro-3-(trifluoromethyl)phenyl]-2-(4-pyridin-3-ylphenyl)hydrazinecarboxamide in the response filed on March 25, 2009 is acknowledged. The traversal is on the grounds: Applicants' claimed compounds all share a common core structural of Formula I that have the same utility of modulating c-Kit or each of the presently pending claims possesses unity of invention. This has not been found to be persuasive because as presented in the office action dated February 9, 2009, prior art exists which causes the core structure to lack a special technical feature, therefore, the feature linking the claims does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the art. Additionally, the variables found on the technical

feature vary extensively and when taken as a whole result in vastly different compounds. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Additionally, the vastness of the claimed subject matter and the complications in understanding the claimed subject matter impose a serious burden on any examination of the claimed subject matter. The claims encompass heteroaryl groups which are variously classified, therefore, "heteroaryl" has been restricted out of the generic embodiment identified for examination. The following is an illustration of the varied classification of the heteroaryl groups: pyrazinyl is classified in class 544 and subclass 336+, pyrimidinyl is classified in class 544 and subclass 242+, pyridinyl is classified in class 546 and subclass 268.1+, etc. Thus, the requirement to restrict the claims (or elect a species) in this application is predicated on the fact that the claimed subject matter involves more than one independent and distinct invention. There is no patentable co-action between the groups and a reference anticipating one member will not render another obvious. Each group is directed to art recognized divergent subject matter which require different searching strategies for each group. Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner.

The examiner will follow the guidelines of MPEP 803.02 wherein once a species is elected, it is examined for compliance with all applicable statutes for patentability and if compliance is found, then the examination is expanded to a reasonable number of elated species to determine whether they also comply with the statute. The examiner

will determine whether the entire scope of the claims is patentable according to MPEP 803.02.

Applicants' elected species appears allowable over the prior art of record. Therefore, according to MPEP 803.02: should no prior art be found that anticipated or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is found that anticipated or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The search of the Markush-type claim has been extended to the non-elected species wherein:

The compounds are of formula **III** (i.e., ring B and C are phenyl; L1 is a single bond; L2 is –XN(R7)C(=O)N(R7)-, -XCH2C(=O)N(R7)- or –CH2XC(=O)N(R7)-; and A is W or is selected from the ring structures disclosed in claims 4 or 16) and the rest of the variables (i.e., G, E, etc.) are as defined in the claims.

As prior art has been found which anticipates the above identified nonelected species, the Markush-type claims are rejected as follows and the subject matter of the claims drawn to nonelected species held withdrawn from consideration. Claims 1-29 have been examined to the extent that they are readable on the elected embodiment and the above identified nonelected species. Since art was found on the nonelected species, subject matter not embraced by the elected embodiment or the above identified nonelected species is therefore withdrawn from further consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of Formulas I, II and III and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for hydrates, prodrugs or metabolites thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The state of the prior art/level of ordinary skill/level of predictability

In regards to polymorphs and hydrates, active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients

can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms, such as polymorphs, solvates and hydrates, are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials.

Therefore, for the reasons above, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al., abstract). In further discussing the predictability of the formation of hydrates or solvates,

Vippagunta et al. discloses that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

"Pro-drugs" are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized *in vivo* into an active metabolite. Wolff et al. (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pages 975-977, 1994) summarizes the state of the prodrug art, the lengthy research involved in successfully identifying a prodrug and the difficulties of extrapolating between species.

The level of skill of the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities as prodrugs. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any prodrug on its face, without evidence to support that particular prodrug. It is noted that the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Each embodiment of a prodrug must be supported by this invention in order to be enabled for the full range of prodrugs of said compounds.

With the limited direction and exemplification the specification offers, it is highly unpredictable that said compounds will actually form effective prodrugs thereof. The

evidence supports the conclusion that the method of making claimed prodrugs is a subject for further study and experimentation.

In regards to metabolites, "metabolites" are commonly known in the art as intermediates and end products of metabolism. There are two different types of metabolites in the art (i.e. primary and secondary). Primary metabolites allow organisms to maintain life by growing, reproducing and sustaining themselves in their environment, whereas secondary metabolites incorporate the use of antibiotics, which are chemotherapeutic agents that inhibit the growth of microorganisms (i.e. bacteria, fungi or protozoa). A metabolite must be biologically active and determining whether a particular compound meets these criteria requires a clinical trial setting and a large quantity of experimentation (i.e., see URL: http: //www.en.wikipedia.org/wiki/Metabolomics). Based on the teachings of the art, it is unclear whether Applicants' invention is drawn to primary or secondary metabolites.

Also, Kwon *et al*. (Handbook of Essential Pharmacokinetics, Pharmacodynamics and Drug Metabolism for Industrial Scientists, 2001, page 213, paragraph 3) discloses the correlation between the rate of metabolite formation and the *in vivo* metabolic clearance of the drug. "Rate data generated from certain *in vitro* systems may underestimate the true metabolic clearance *in vivo* owing to limitations in discerning metabolic capability."

The amount of direction or guidance present/existence of working examples

A disclosure should contain representative examples which provide reasonable

assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. The specification does not adequately enable a method of making the prodrugs, hydrates or metabolites of the compounds that the claims encompass.

There is no data present or any working examples in the specification for the preparation of prodrugs, hydrates or metabolites of said compounds.

As discussed above, it would be necessary for Applicants to provide evidentiary support for each embodiment due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others.

Breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include any prodrugs, hydrates or metabolites of said compounds.

The quantity of experimentation needed

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare any hydrate, prodrug or metabolite of said compounds.

The specification provides limited support, as noted above, for the prodrugs, hydrates or metabolites encompassed by the claims. The quantity of experimentation needed to make the prodrugs, hydrates or metabolites encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons stated above. Even with the undue burden

of experimentation, there is no guarantee that one would obtain the desired prodrugs in view of the Wolff et al. reference. Also, the science of crystallization has evolved such that, without guidance or working examples in the specification, the claim lacks enablement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claim 25 recites the definition of "R3," however, R3 is not a substituent in formula **III** (i.e., "R30" is), therefore, there is insufficient antecedent basis for this limitation in the claim. It is believed that Applicants meant "R30" and not "R3" and the examiner has examined the claim as such for the purposes of this office action. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 15-18, 21-23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/52906.

Specifically, WO 99/52906 discloses the compound of example number 44 (Table 1, page 31) which anticipates a compound of the instant claims or a compound of formula **III** wherein W is 1,3-thiazole, E is O, G is CH2, R30 is H, and R27 is substituted heterocyclyl.

Claims 1, 2, 4-10, 16-18, 21, 22, 24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/06246.

Specifically, WO 02/06246 discloses compounds which are used in pharmaceutical compositions (i.e., abstract), such as the compound of example number 99 (Table 1, page 53) which anticipates a compound of the instant claims or a compound of formula **III** wherein W is phenyl, E is CH2, G is NH, and R30 is substituted heterocyclyl.

Claims 1-7, 9, 10, 15-18, 21, 22, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Soliman et al. (Journal of Pharmaceutical Sciences, Vol. 70, No. 6, June 1981).

Specifically, Soliman et al. discloses compounds which are used in pharmaceutical compositions (i.e., abstract), such as compounds Ve (Table I, page 603) and VIIIe (Table II, page 604) which anticipate compounds of the instant claims or compounds of formula **III** wherein E is S(O)2, G is NH, R30 is H, W is pyrazole, and R27 is phenyl and methyl (i.e., compound Ve) or R27 is phenyl, methyl and halogen (i.e., compound VIIIe).

Claims 1-11, 15-18, 21, 22, 24, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Ashton et al. (Journal of Medicinal Chemistry, 1973, Vol. 16, No. 5).

Specifically, Ashton et al. discloses compounds which are used in pharmaceutical compositions (i.e., abstract), such as compound number 12 (Table II, page 454) which anticipates a compound of the instant claims or a compound of formula **III** wherein E is CH2, G is NH, R30 is halogen, W is pyrimidine, and R27 is R(R55)R55 wherein R55 is hydrogen and methyl.

Claims 1-10, 15-18, 21, 22, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Beilstein Registry Number 8640850 (Meyer et al.).

Specifically, Meyer et al. discloses a compound (i.e., Beilstein Registry Number 8640850) which anticipates a compound of the claims or a compound of formula **III** wherein E is CH2, G is NH, R30 is H, W is oxazole, and R27 is phenyl.

Claims 1-7, 9-11, 15-18, 21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Patent Compound Registry Number 1495354 (i.e., US5814631 A1).

Specifically, US5814631 A1 discloses a compound (i.e., Patent Compound Registry Number 1495354) which anticipates a compound of the claims or a compound of formula **III** wherein E is S(O)2, G is NH, W is tetrazole, and R30 is halogen and CO2R40 wherein R40 is methyl.

Claims 16-18, 21, 22, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Auzou et al. (European Journal of Medicinal Chemistry (1984), 19(3), 283-4).

Specifically, Auzou et al. discloses compounds which are used in pharmaceutical compositions (i.e., abstract), such as a compound wherein one of R1, R2 or R3 is OCHMeCONH-pCl-C6H4 with no other substitution on the Ph ring which anticipates a compound of the claims or a compound of formula **III** wherein E is O, G is C(R31)R32 wherein R31 or R32 is hydrogen with the other being methyl, R30 is halogen, W is pyrrole, and R27 is methyl.

Claim Objections

Claims 1-29 are objected for containing non-elected subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIN BIANCHI whose telephone number is (571)270-5232. The examiner can normally be reached on Mon-Fri 7am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kamal A Saeed/
Primary Examiner, Art Unit 1626

Kristin Bianchi
Examiner
Art Unit 1626

***